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APPLICANTS:	Strominger et al.		
SERIAL NO.:	08/991,628	GROUP NO.:	1644
FILING DATE:	November 5, 1997	EXAMINER:	DiBrino, M.
TITLE:	Preparations for Inducing Immunotolerance and Uses Therefor		

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The Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

APPLICANT'S BRIEF ON APPEAL TO THE

BOARD OF PATENT APPEALS AND INTERFERENCES

This is Applicant's Brief (submitted in triplicate as required by 37 C.F.R. 1.192) in support of an appeal to the Board of Patent Appeals and Interferences from the final rejection of claims 3-6, 11, and 13-16 in the above-referenced application. Also enclosed are Appendices A-D which are referenced and relied upon herein.

A Notice of Appeal was submitted to the U.S. Patent Office on December 21, 2000, in which Appellant appealed the final rejection of claims 3-6, 11, and 13-16 in the Office Action, made final, dated July 3, 2000. A five-month extension of time up to and including Monday, July 23, 2001 for filing this Appeal Brief is respectfully requested. A petition for the extension of time and the requisite fee are submitted herewith.

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REAL PARTY IN INTEREST

The Real Party in Interest is the President and Fellows of Harvard College, Cambridge, Massachusetts by virtue of an assignment from the inventors of the parent application, USSN 08/400,796 which issued as U.S. Patent No. 5,874,531, which was recorded at Reel 7540, Frame 0884 on May 15, 1995. [Confirm that Harvard is the Real Party in Interest.]

RELATED APPEALS AND INTERFERENCES

The Applicant's undersigned legal representative is unaware of another appeal or interference which will directly affect, or be directly affected by, or have a bearing on the Board's decision in this pending appeal.

STATUS OF CLAIMS

Claims 3-6, 11, and 13-16 are pending in the above-identified application and are the subject of this appeal. Claims 1, 2, 7-10, 12, 17-29 are cancelled. In response to an election of species requirement, Applicants elected SEQ. ID. NO. 3 as the peptide species and pemphigus vulgaris as the autoimmune disease condition species. Claims 3-6, 11, and 13-16 are set forth in the attached Appendix A.

STATUS OF AMENDMENTS

No amendments were filed subsequent to the Final Office Action mailed from the U.S. Patent Office on July 3, 2000. All previous amendments have been entered.

SUMMARY OF THE INVENTION

Applicants provide the following concise summary of the invention.

The specification states, at page 6, lines 20-31 that: "The present invention provides, in one aspect, pharmaceutical preparations for use in tolerizing individuals to autoantigens. The preparations include a pharmaceutically acceptable carrier and an isolated human polypeptide which includes an amino acid sequence corresponding to a sequence motif for an HLA-DR protein which is associated with a human autoimmune disease. These polypeptides are capable of binding to the HLA-DR protein to form a complex which activates autoreactive T cells in subjects having the autoimmune disease. The peptides are not derived from human collagen or human myelin basic protein."

The specification states, at page 7, lines 1-10: "In particular embodiments, such pharmaceutical preparations are provided in which the HLA-DR protein is HLA-DR4 protein and the autoimmune disease is pemphigus vulgaris. In addition, a particular sequence motif is provided for pemphigus vulgaris and pharmaceuticals having peptides with this motif are provided. Specific embodiments of the pharmaceuticals include each of the polypeptides described above with respect to pemphigus vulgaris. Thus, methods of tolerizing an individual to a pemphigus vulgaris autoantigen are also provided."

The specification states, at page 7, lines 11-21: "In another set of embodiments, the invention provides for pharmaceutical preparations for use in tolerizing individuals to antigens of human pathogens which are implicated in human autoimmune disease. The preparations include a pharmaceutically acceptable carrier and an isolated human pathogen polypeptide which includes an amino acid sequence corresponding to a sequence motif for an HLA-DR protein which is associated with a human autoimmune disease. These polypeptides are capable of binding to the HLA-DR protein to form a complex which activates autoreactive T cells in subjects having the autoimmune disease."

The specification states, at page 8, lines 1-14: "In another aspect of the invention, pharmaceuticals are provided for vaccination against a human pathogen implicated in the aetiology of autoimmune disease. These pharmaceutical preparations include a pharmaceutically acceptable carrier and an immunogenic preparation effective to immunize against a human pathogen. The human pathogen is one which in its native form includes a polypeptide having an amino acid sequence corresponding to a sequence motif for an HLA-DR protein which is associated with the autoimmune disease. These polypeptides are capable of binding to the HLA-DR protein to form a complex which activates T cells which become autoreactive and initiate the autoimmune disease. The preparations of the present invention specifically do not include such polypeptides but, rather, include other antigens from the pathogen."

The specification states, at page 8, lines 14-24: "In particular embodiments, such pharmaceutical preparations are provided in which the HLA-DR protein is HLA-DR4 protein and the autoimmune disease is pemphigus vulgaris. In addition, a particular sequence motif is

provided for pemphigus vulgaris and pharmaceuticals which lack peptides having this motif are provided. Specific embodiments of the pharmaceuticals include preparations lacking each of the polypeptides described above with respect to pemphigus vulgaris."

Although those teachings are summarized above, the Board is strongly urged to study the specification before considering the rejections on appeal. A copy of the specification is attached as Appendix B. A copy of the parent application, U.S. Serial No. 08/400,796, which issued as U.S. Patent No. 5,874,531 on February 23, 1999, is attached as Appendix C.

ISSUES

1. The first issue presented for appeal is whether claims 3-6, 11, and 13-16 are unpatentable under 35 U.S.C. §112, 1st paragraph rejection as being based on a nonenabling disclosure.

2. The second issue presented for appeal is whether claims 13-16 are unpatentable under 35 U.S.C. §112, 1st paragraph rejection as being indefinite.

3. The third issue presented for appeal is whether the double patenting rejection over claim 3 of U.S. Patent No. 5,874,531 is proper.

4. The fourth issue presented for appeal is whether appealed claims 3-6, 11, and 13-16 are patentable over Amagai et al. (*Autoantibodies against a Novel Epithelial Cadherin in Pemphigus Vulgaris, a Disease of Cell Adhesion*, Cell Vol., 67, 869-877 (1991), hereinafter "Amagai") under 35 U.S.C. §102.

5. Although Applicant believes that the above-identified issues correspond to all of the pending rejections, Applicants also appeal any other bases for rejection of the pending claims which were not explicitly stated in the Final Office Action, but which may be regarded as still pending.

GROUPING OF CLAIMS

Rejected claims 3-6 stand or fall together, claim 11 stands or falls alone, and claims 13-16 stand or fall together.

ARGUMENT

Pursuant to 37 C.F.R. §1.192(c)(8)(iv), the following sections discuss the legal standard applicable to the instant application, indicate the specific limitations in the rejected claims which are not disclosed in the applied references, and explain how such limitations render the claimed subject matter patentable.

Autoimmune disease is generally defined as the pathological consequences, including tissue injury, produced by autoantibodies or autoreactive T cells interacting with self epitopes. An "epitope" is defined as an antigenic determinant ... the simplest form or smallest structural area on a complex antigen molecule that can combine with an antibody or T lymphocyte receptor." (The Illustrated Dictionary of Immunology, CRC Press (1995)) Self epitopes are derived from an individual's own proteins. Such an inappropriate response of the immune

system against self-components can cause serious damage to cells and organs, sometimes with fatal consequences.

The distinction between an antigen and an epitope is critical to the understanding of the present invention. The terms "autoantigen," and "self antigen," as understood in the art and used in the instant specification refers to full-length protein or polypeptide that includes a self epitope which, as stated above, is the simplest form or smallest structural area on a complex antigen molecule that can combine with an antibody or T lymphocyte receptor.

T cell recognition of antigens, including self antigens, involves a tri-molecular complex of (1) a T cell receptor, (2) an MHC molecule, such as HLA-DR, and (3) a short peptide comprising an epitope. (See for example, page 6, lines 27-30, original claims 3 and 13, and pending claims 3 and 13 which require the that the polypeptides of the invention be "capable of binding to HLA-DR protein to form a complex which activates autoreactive T cells in subject having the autoimmune disease.") When the MHC molecule is a Class II molecule, such as HLA-DR, the peptides derived from antigen are heterogeneous in size. (See page 5, lines 8-10.) Peptides that bind HLA-DR molecules have been reported as ranging in size from 12-25 amino acid long. (See Chicz et al. *Predominantly naturally processed peptides bound to HLA-DR1 are derived from MHC-related molecules and are heterogeneous in size*, Nature 358:764-768 (1992), cited on page 5, at line 10 of the original specification.)

Particular MHC class II molecules (e.g., HLA-DR) have been associated with autoimmune disease. For example, HLA-DR4 has been associated with the autoimmune

condition pemphigus vulgaris (PV). PV is an autoimmune disease of the skin which is manifested by blistering lesions of the skin and mucous membranes. (See page 2, lines 13-17.)

The present specification teaches methods of identifying peptides that form part of the tri-molecular complex with autoreactive T cells and HLA-DR molecules. Such peptides are useful to treat autoimmune diseases, for example, by inducing high dose tolerance to thereby render autoantigenic T cells unresponsive to self epitope bound to an HLA-DR molecule. (See page 30, lines 14-31 and page 52, lines 11-15.)

A large body of clinical and epidemiological evidence suggests that bacterial or viral infection may trigger the induction of autoimmunity. (See page 3, lines 13-17.) One theory is that peptides of the pathogen that closely resemble self peptide "mimic" self epitopes to activate autoreactive T cells and induce autoimmunity. Accordingly, the present invention also provides for methods of vaccinating an individual against an autoimmune condition by vaccinating the individual with antigens or peptides from the pathogen while specifically excluding peptides from the pathogen that form part of the complex with autoreactive T cells and HLA-DR molecules. (See page 32, lines 9-29.)

Issue 1 - Rejections Under 35 U.S.C. §112, First Paragraph

Claims 3-6, 11 and 13-16 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to meet the enablement requirement. In particular, the Office Action suggested that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to make/use the invention.

The Office Action states that "the specification, while being enabling for a pharmaceutical preparation comprising a human polypeptide *consisting* of one of SEQ IDS NOS: 1-7, does not reasonably comprise a human polypeptide *consisting essentially* of an amino acid sequence corresponding to the core MHC binding residues of a sequence motif for an HLA-DR protein, nor *consisting essentially of* one of SEQ ID NOS: 1-7, nor a polypeptide *having* an amino acid sequence corresponding to the core MHC binding residues of a sequence motif for an HLA-DR protein." (Emphasis added.)

Applicant's Rebuttal of Rejection of Claims 3-6 and 11 under 35 U.S.C. §112, First Paragraph

According to the MPEP 2111.03, the transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. *In re Herz*, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976) (emphasis in original) Furthermore, "A 'consisting essentially of' claim occupies a middle ground between closed claims that are written in a 'consisting of' format and fully open claims that are drafted in a 'comprising' format." *PPG Industries v. Guardian Industries*, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir. 1998).

"For search and examination purposes, *absent a clear indication in the specification of what the basic and novel characteristics actually are*, 'consisting essentially of' will be construed as equivalent to 'comprising.'" See, e.g., *PPG*, 156 F.3d at 1355, 48 USPQ at 1355 (Emphasis added.) However, when there is a clear indication in the specification of what the basic and novel characteristic are, "the "consisting essentially of" terminology would ... *exclude*

additional unspecified ingredients which would affect the basic and novel characteristics of the product defined in the balance of the claim." *In re Garnero*, 162 USPQ 221, 223 (C.C.P.A. 1969) (Emphasis added.)

As explained below, Applicants have clearly indicated the basic and novel characteristics of the present invention in the instant specification and therefore the "consisting essentially of" phrase should be construed as open to those materials that do not materially affect the basic and novel characteristics and closed to those materials that do materially affect the basic and novel characteristics of the claimed invention.

In brief, the present application teaches methods of "defining those amino acids of the self or non-self antigen that are needed for MHC binding and TCR [T cell receptor] contact" so that "self epitopes involved in autoimmune disease may be identified." (See page 5, lines 24-31.) It is these self epitopes (and non-self epitopes that mimic self epitopes) that are the active agents of the pharmaceutical preparations for tolerization recited in claims 3-6. Accordingly, the basic and novel characteristics of the claimed polypeptides include the ability (1) bind to HLA-DR protein and (2) activate autoreactive T cells from a subject having an autoimmune disease.

Applicants submit that independent claim 3 (as well as claims 4-6 and 11 which depend from claim 3) which claims polypeptides that "consist essentially of an amino acid sequence corresponding to the core MHC binding residues of the sequence motif for an HLA-DR molecule ... [which] binds to said HLA-DR protein [and] activates autoreactive T cells from a subject having said autoimmune disease" embrace only polypeptides the bind to HLA-DR and activate

autoreactive T cells and exclude peptides that are incapable of binding to HLA-DR and/or activating autoreactive T cells.

Furthermore, the specification expressly states that "peptides including at least the MHC binding and TCR contact residues are contemplated as equivalents." (See page 28, lines 27-30.) Thus, the present specification clearly indicates that the basic and novel characteristics of the claimed polypeptides are the ability to (1) bind to HLA-DR protein and (2) activate autoreactive T cells from a subject having an autoimmune disease. Accordingly, Applicants submit that the instant specification fully enables pending claims 3-6 and 11 when the term "consisting essentially of" is interpreted properly as partially open and partially closed. Under this construction of the "consisting essentially of" phrase, claims 3-6 and 11 include polypeptides with an amino acid sequence corresponding to the core MHC binding residues of a sequence motif for HLA-DR protein and other components (e.g., additional amino acids) that do not materially affect the ability of the polypeptides to bind to HLA-DR molecules and activate autoreactive T cells from a subject having an autoimmune disease.

Full length proteins or long peptides do not fall within the scope of the claims 3-6 and 11 because, as was notoriously well known in the art at the time the application was filed, MHC molecules do not bind full length proteins or long peptides from an antigen but rather, MHC molecules bind short peptides that are small fragments of an antigen. The distinction between an antigen and an epitope is critical to the understanding of the present invention. The terms "autoantigen," and "self antigen," as understood in the art and used in the instant specification refers to full-length protein or polypeptide that includes a self epitope. As stated above, an

"epitope" is an antigenic determinant ... the simplest form or smallest structural area on a complex antigen molecule that can combine with an antibody or T lymphocyte receptor.

The present application is directed to identification of self epitopes and preparations that utilize such self epitopes. The present specification explains that although the target antigens implicated in the immunopathogenesis of disease have been identified, specific self epitopes have not been identified. See, for example, page 23, lines 15-20, which reads: "An ever increasing number of autoimmune diseases are now being associated with particular alleles of the MHC class II HLA-DR locus. For most of these autoimmune diseases, the self epitope remains unknown. For some, however, the self protein involved in autoimmune response is known or suspected. In one aspect of the present invention, a method is provided for identifying the self epitopes involved in autoimmune diseases associated with HLA-DR alleles." (Emphasis added.) The pharmaceutical preparations of claims 3-6 and the method of claim 11 utilize these self epitopes to tolerize (i.e., render autoreactive T cells unresponsive to the self epitope when bound to an presented by an MHC molecule, page 52, lines 12-17) an individual to an autoantigen. Furthermore, the preparation of claims 13-16 removes these self epitopes from a preparation to vaccinate an individual against a pathogen associated with autoimmune disease.

The specification reiterates the distinction between an autoantigen and self epitope with regard to the autoimmune disease pemphigus vulgaris at page 37, lines 16-23 "Although the autoantigen for pemphigus vulgaris is known, the precise epitopes within the autoantigen have previously remained unknown. Using the methods of the present invention, it has been possible to identify a small set of peptides that may serve as the autoantigenic determinants. The target

antigen of pemphigus vulgaris is an epithelial adhesion molecule of the cadherin family, desmolgein 3 (Amagai et al. 1991)." As stated in the Abstract, "The peptides relating to pemphigus vulgaris are self epitopes," thus, the polypeptides recited in claims 3-6 and 11 are essentially self epitopes which form part of the HLA-DR/T cell receptor/peptide complex that causes autoimmune disease as such, they are necessarily relatively small peptides.

Furthermore, the working examples of the polypeptides of the invention that are disclosed in the instant specification (SEQ. IDS NO. 1-7) and recited in claims 6 and 16 are peptides that are 15 amino acids long, "partly as a result of the computer database search program used (Genetics Computer Group program "Findpatterns") but also *corresponding to the size of the cleft in MHC class II molecules*." (See page 37, lines 10-14) Thus, the instant specification teaches that polypeptides capable of binding to HLA-DR proteins may be approximately 15 amino acids long. However, the instant specification also teaches that shorter or longer peptides "may have utility" and thus, "fall within the spirit and the scope of the claims" See page 28, lines 16-30. Thus, pending claim 3 which recites a pharmaceutical preparation for tolerization ... consisting essentially of an amino acid sequence corresponding to the core MHC binding residues of a sequence motif for an HLA DR protein, ... [which] binds to said HLA-DR protein [and] activates autoreactive T cells" embraces polypeptides that consist of self epitopes (which may be heterogeneous in size) and excludes full length proteins and large protein fragments that are too large to form the HLA-DR/T cell receptor/peptide complex.

Applicant's Rebuttal to the Rejection of Claims 13-16 under 35 U.S.C. §112, First Paragraph

The Office Action alleges that claim 13 is not enabled for preparations for immunizing an individual against a "human pathogen that in its native form includes a polypeptide having an amino acid sequence corresponding to the core MHC binding residues of a sequence motif for an HLA-DR protein."

"Transitional phrases such as "composed of," "having," or "being" must be interpreted in light of the specification to determine whether open or closed claim language is intended. See, e.g., Regents of the Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 1573, 43 USPQ2d 1398, 1410 (Fed. Cir. 1997), cert. denied, 118 S. Ct. 1548 (1998) (In the context of a cDNA having a sequence coding for human PI, the term "having" still permitted inclusion of other moieties.). MPEP 2111.03

Applicants note that the objected to phrase recited in claim 13 sets forth the target of the immunization, a pathogen that in its native form includes polypeptides having amino acid sequence corresponding to the core MHC binding residues of a sequence motif and the final limitation of the claim requires that the pharmaceutical preparation be free of the amino acid sequence corresponding to the core MHC binding residues. Accordingly, applicants submit that the phrase "having" as used in claim 13 is an open transitional phrase, which includes polypeptides native to the pathogen. However, the "free of the amino acid sequence corresponding to the core MHC binding residues" limitation excludes epitopes that bind to HLA-DR and activate autoreactive T cells. For the foregoing reasons, Applicants submit that claim 13

and claims 14-16 which depend from claim 13 clearly recite the preparation for vaccinating an individual at risk of autoimmune disease disclosed in the instant specification.

Applicant's Rebuttal to the Rejection of Claims 3-6, 11, and 13-16 under 35 U.S.C. §112, First Paragraph

The Office Action suggests that claims 3-6, 11, and 13-16 are nonenabled because (1) "there is no guidance in the specification as to what alterations result in a functional polypeptide, i.e., one that binds HLA-DR", (2) "extended experimentation would be required to determine which substitutions would be required to determine which substitutions would be acceptable to retain functional activity" and (3) "the relationship between the sequence of a peptide and its tertiary structure (i.e., its activity) are not well understood and are therefore not predictable."

Regarding the first basis for the rejection, applicants submit that the present specification does provide detailed analysis of the binding pockets of HLA-DR molecules, teaches the skilled artisan how to predict what peptides are capable of binding to HLA-DR molecules. For example, the binding motif recited in claims 5 and 15 provides explicit guidance for peptides capable of binding to HLA-DR molecules.

Regarding the second issue indicated above, applicants note that "The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." In re Angstadt, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Moreover, applicants submit that neither "extensive experimentation" nor "undue experimentation" is required to practice the claimed invention. Applicants submit that the identification of amino

acid sequences that have functional activity including the ability to bind to HLA-DR proteins and to activate autoreactive T cells maybe readily determined by various assays that were well known to the skilled artisan including, for example, the T cell proliferation assay that is described in Example 1 of the instant specification at page 44, lines 11-22.

The MPEP 2164.01(a) states: "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." In re Certain Limited-Charge Cell Culture Microcarriers, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). The specification further teaches, at page 25, lines 3-13, that the peptides of the invention may be screened for activity using experimentation that is typical in the art, for example, by "*in vitro* tests for the ability to induce proliferation of autoreactive T cells or to induce the secretion of lymphokines (cytokines) form these T cells or to induce other effector functions such as cytotoxicity." Accordingly, applicants submit that undue experimentation is not required to practice the claimed invention.

Finally, applicants submit that the tertiary structure of self epitopes does not materially impact the ability of a self epitope polypeptide to bind to HLA-DR molecules and activate autoreactive T cells. The Office Action cites the Ngo et. al reference (*The Protein Folding Problem and Tertiary Structure Prediction*, Merz & LeGrans, Birkhauser, Boston, pages 491-495, 1994) to support the assertion that the relationship between the sequence of a peptide and the tertiary structure is not predictable. Applicants submit that the Ngo reference is not relevant to the present invention because, as is well known in the art, proteins are cleavage into fragments

of approximately 12-25 amino acids and bound in the binding cleft of the HLA-DR molecule in an unfolded or essentially linear conformation. See page 116 of Cellular and Molecular Immunology, attached at Appendix D, which states "T cells recognize only linear determinants of peptides defined predominantly by primary amino acid sequences that assume extended confirmations within the peptide-binding clefts of MHC molecules." Accordingly, applicants submit that the difficulties in predicting the folding pattern or tertiary structure of a full length protein discussed in Ngo is irrelevant to the ability of the peptides of the invention to bind to HLA-DR molecules.

Therefore, in light of the foregoing reasons, Applicants respectfully request that the rejections under 35 U.S.C. §112, first paragraph, be reconsidered and withdrawn.

Issue 2 - Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 13-16 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In particular, the Office Action suggests that the recital of the phrase "wherein said preparation is free of a polypeptide corresponding to said sequence" is unclear. Applicants submit that claim 13 clearly claims a pharmaceutical for vaccinating an individual at risk of an autoimmune disease by vaccinating against a human pathogen with pathogenic polypeptides which specifically excludes pathogenic polypeptide corresponding to a sequence motif for HLA-DR protein associated with an autoimmune disease. The text of claim 13 reads as follows:

13. A pharmaceutical preparation for vaccinating an individual at risk of an autoimmune disease comprising a pharmaceutically acceptable carrier and

an amount of an immunogenic preparation effective to *immunize against a human pathogen that in its native form includes a polypeptide having an amino acid sequence corresponding to the core MHC binding residues of a sequence motif for an HLA-DR protein*;

wherein said sequence motif for said HLA-DR protein is based upon the structure of the HLA -DR binding site

wherein said HLA-DR protein is associated with said autoimmune disease;

wherein said polypeptide binds to said HLA-DR protein;

wherein said polypeptide bound to said HLA-DR protein activates autoreactive T cells from a subject having said autoimmune disease; and

wherein said preparation is *free of a polypeptide corresponding to said sequence*. (Emphasis added.)

The Office Action suggests that the phrase "free of a polypeptide corresponding to said sequence" is indefinite. Applicants submit that this phrase is amenable to a single interpretation, that is, that the amino acid sequences present in the native protein or polypeptide profile of the pathogenic organism which that bind to HLA-DR and activate autoreactive T cells are not present in the pharmaceutical preparation. The Office Action further suggests that the recitation of "includes a polypeptide" is unclear because it is not clear whether said polypeptide is a portion of a protein from a pathogenic organism. This phrase, taken in the full context of the limitation "immunize against a human pathogen that in its native form includes a polypeptide having an amino acid sequence corresponding to the core MHC binding residues of a sequence motif for an HLA-DR protein" clearly indicates that the polypeptide recited in claim 13 is a portion of a protein from the pathogenic organism.

Applicants submit that claim 13 satisfies the requirements of 35 U.S.C. §112, second paragraph, respectfully request that the rejection of claim 13 and claims 14-16, which depend from claim 13 under 35 U.S.C. §112, second paragraph, be reconsidered and withdrawn.

Issue 3 - Double Patenting

Claims 3-6 and 13-16 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3 of U.S. Patent No. 5,874,531. The Office Action states that "although the conflicting claims are not identical, they are patentably indistinct from each other because the composition comprising the peptides of claim 3 of the '531 patent are encompassed by the instant claims. Applicants note that the instant application is a division of the application that issued as the '531 patent and as such, 35 U.S.C. § 121 prohibits the use of the '531 patent as a reference against the instant application.

Issue 4 - Rejections Under 35 U.S.C. §102

Claims 3-5 and 13-15 were rejected under 35 U.S.C. §102 as being anticipated by Amagai. The Office Action states that "in the absence in the specification of a definition of a 'human polypeptide consisting essentially of ...', the claim language is open, and inclusive of the full-length autoantigen."

As stated above, with regard the §112, first paragraph rejection, applicants submit that the specification clearly indicates what are the basic and novel characteristics of the invention, and the transitional phrase is therefore partially open and partially closed.

The disclosed invention provides a binding motif to determine which residues of a putative antigenic protein are capable of binding autoimmune associated HLA-DR proteins and activating autoreactive T cells. As stated above, independent claims 3 and 13 are intended to embrace polypeptides capable of binding autoimmune associated HLA proteins, not a full-length autoantigenic protein as described in Amagai. Thus, applicants submit that Amagai fails to teach or even suggest the invention recited in claims 3-6, 11, and 13-16.

Although Amagai teaches that desmoglein 3 is the full length autoantigen for pemphigus vulgaris, Amagai fails to teach or even suggest what short peptides make up the self epitopes for pemphigus vulgaris. Applicants submit that inclusion of the full-length 103 kD pemphigus vulgaris antigen protein disclosed by Amagai in the preparations of claim 3 would materially affect the basic and novel characteristics of the preparation and, therefore, the full-length pemphigus vulgaris protein is excluded from the scope of independent claim 3. Applicants further submit that one of ordinary skill in the art would readily recognize that a preparation for tolerization consisting essentially of an isolated peptide capable of binding to HLA-DR and activating autoreactive T cells is superior to a preparation containing a full-length protein.

Applicants further submit that Amagai fails to anticipate pending claims 13-16 for the following reasons. Independent claim 13 recites, in part, a vaccination preparation "that in its native preparation includes a polypeptide having an amino acid sequence corresponding to a

sequence motif for an HLA-DR protein ... wherein said preparation is free of a polypeptide corresponding to said sequence" amino acid sequence corresponding to a sequence motif for an HLA-DR protein." Amagai fails to teach a vaccination preparation which includes antigenic polypeptides of a pathogen and excludes polypeptides that activated autoreactive T cells from a subject having an autoimmune disease. Thus, Amagai does not anticipate these claims.

In conclusion, Applicants submit that independent claims 3 and 13 are not anticipated by Amagai. Applicants further submit that Amagai does not anticipate claims 4-6, 11, and 12-16 which depend from claim 3 and 13, respectively. In light of the foregoing, Applicants respectfully request that the 35 U.S.C § 102 rejection of claims 3-6, 11, and 13-16 be reconsidered and withdrawn.

5. The Claimed Invention Is Not Unpatentable Under Any Other Possible Bases for Rejections

Applicant believes that the foregoing arguments address each of the pending rejections of the pending claims. In particular, the present Brief addresses each of the rejections made in the Final Office Action. However, if the Examiner regards any of other rejections as currently pending, Applicant requests that any and all such rejections be raised in the Examiner's Answer so that Applicant has an opportunity to respond.

CONCLUSION

For the reasons given above, it is respectfully urged that the final rejections be reversed and the application be passed to issue with claims 3-6, 11, and 13-16.

A Petition and Fee for the filing of this Brief on Appeal, as well as a Petition and Fee for a five-month Extension of Time for Response, is submitted herewith. Applicants believe that no other fees are necessitated by the present filing. However, in the event that any additional fees are due, the Commissioner is hereby authorized to charge any such fees to Attorney's Deposit Account No. 20-0531.

Respectfully submitted,

Date: July 23, 2001
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